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EXAMINER	
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ART UNIT	PAPER NUMBER
1641	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/582,090	IMAI, KAZUHIRO	
	Examiner	Art Unit	
	Leon Y. Lum	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-21 and 24-26* is/are pending in the application.

4a) Of the above claim(s) *24 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-20 and 26* is/are rejected.

7)☒ Claim(s) *21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 April 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/15/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

Claims 24 and 25 are objected to because of they have an improper status identifier. Since these claims are withdrawn, their status should be "Withdrawn." Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-7, 9, 15 and 26 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 7,179,655 to Patricelli.

i. Independent claims 1 and 15 are anticipated

Patricelli describes a screening and identifying method that comprises, as the screening step, labeling target proteins with a fluorescently labeled activity based probe (ABP), digesting and separating the ABP-labeled. *See* column 2, lines 35-46 and column 15, lines 53-67. Accordingly, Patricelli teaches the converting step as claimed. The separating can be performed using an HPLC. *See* column 20, lines 57-59. The

screening step can include fluorescence detection. *See* column 19, lines 44-56 and column 20, lines 35-43. Patricelli therefore teaches the first separating step.

Regarding the first applying step, Patricelli teaches this phrase because the identifying step of the method sends separated ABP-labeled proteins for mass spectrometry. *See* column 21,lines 37-50.

Regarding the first separating and applying steps, Patricelli teaches that "the labeled ABP-active target protein conjugates are most preferably proteolytically digested prior to the next stage of enrichment and/or analysis," (emphasis added) in which the enrichment is the "liquid chromatography and/or electrophoresis" separations. *See* column 5, lines 23-25 and 31-33. While this indicates that digestion is preferably performed before separation, the phrase also implies that the digestion can be performed after separation. Indeed, by reciting "most preferably," the phrase indicates that, although not preferred, the ABP-active target protein can first be separated and then digested. Moreover, the digestion can be performed using trypsin, which, according to the Specification on page 6, section (6), produces enzymatic hydrolysis. *See* column 20, lines 57-59. Accordingly, Patricelli implicitly describes a separation step prior to the enzymatic hydrolysis step.

Patricelli states that a separation technique during the identification step is something that may be used. *See* column 21, lines 51-54. Accordingly, Patricelli teaches the second separating step.

Patricelli also teaches that MS-quantified peptides can be correlated with a sequence database, thereby teaching the collating and providing steps. *See* column 22, lines 31-33.

ii. Claims 2-7, 9 and 26 are anticipated

Regarding claims 2 and 3, Patricelli teaches HPLC separation combined with fluorescence detection, and submitting the separated proteins for mass spectrometry. *See supra* rejection of claim 1. Patricelli also describes that each of the identification and separation steps can include a chromatography step. *See* column 15, line 60 to column 16, line 2 and column 21, lines 51-60.

Regarding claim 4, Patricelli describes a fluorescent ABP label with an affinity for an active site on a protein. *See* column 9, lines 27-29.

Regarding claims 5, Patricelli describes electrophoresis separation. *See* column 19, line 50.

Regarding claim 6, Patricelli teaches trypsin, as described above. *See supra* rejection of claim 1.

Regarding claim 7, Patricelli describes a RP-HPLC. *See* column 20, lines 57-59.

Regarding claim 9, Patricelli describes a biological sample. *See* column 5, lines 38-51.

Regarding claim 26, Patricelli teaches that the fluorescent fractions are preferably digested first and then separated before mass spectrometry. *See supra* rejection of claim 1. Although the claim does not require a digestion and separation step, it does not exclude it either. Indeed, the claim includes “comprising” language.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Patricelli, cited above, in view of U.S. Patent No. 6,629,040 to Goodlett *et al*. ("Goodlett").

Patricelli does not explicitly recite a database containing fluorescent reagent-labeled amino acid data. However, Patricelli does disclose a database containing protein fragment data for comparison purposes. Moreover, Patricelli specifically describes performing an analysis on "labeled peptide samples." *See* column 22, lines 33-38.

Goodlett describes comparing the mass of digested and labeled peptides to those in a database. *See*, for example, claim 7.

It would have been obvious to one of ordinary skill in the art to modify Patricelli's method by including fluorescent-labeled amino acid data in the database, as taught by Goodlett. The skilled artisan would have performed the modification because doing so would provide a database with a more accurate comparison between peptides since the sample peptides are labeled. Moreover, since Patricelli teaches a database, the skilled artisan would have had a reasonable expectation of success in updating the database.

Claims 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patricelli, cited above, in view of U.S. Patent No. 6,653,625 to Andersson *et al*. ("Andersson").

i. Claim 11 is obvious

Patricelli, described above, teaches a labeling step, a separating step comprising an HPLC separation step prior to protease digestion by trypsin and an identification step comprising a separating procedure prior to mass spectrometry analysis. The separating steps can be performed using HPLC combined with fluorescent detection. Together, these steps comprise a series of four steps that, in sequence, fluorescently label a protein sample, separate the sample using HPLC chromatography with fluorescent detection, digest the sample using trypsin and separate the sample again using HPLC chromatography with fluorescent detection. Moreover, Patricelli describes a database for comparing experimental results with known peptide structures. A computer is

necessary to store the database; hence, Patricelli teaches "one...type of structural analysis device equipped with a database containing data on amino acids labeled with the fluorescent reagent.

Patricelli, however, does not teach a separate physical embodiment to perform each of the four steps above.

Andersson describes a microfluidic system comprising multiple channel parts including a reaction zone for digestion and a separating zone using chromatography. *See* column 7, lines 10-30. However, Andersson does not limit the system to just one reaction zone and separation zone. Indeed, each channel can comprise “one or more channel parts" that function as a reaction zone and separation zone. *Id*. Moreover, the microfluidic system can efficiently transform a sample for mass spectrometry analysis while maintaining a reproducible yield and minimal loss of material. *See* column 3, lines 3-8. The microfluidic system also includes an outlet connected to a mass spectrometry device. *See* column 6, lines 9-22.

Given the foregoing description, it would have been obvious to one of ordinary skill in the art to modify Andersson’s device by incorporating a separate chamber for each of Patricelli’s steps. The combination, therefore, will produce a distinct labeling chamber, first HPLC separation channel with a fluorescent detector, a digestion chamber and a second HPLC separation channel with a fluorescent detector. The skilled artisan would have been motivated to perform the modification because a microfluidic device can efficiently transform a sample for mass spectrometry analysis while maintaining a reproducible yield and minimal loss of material. Moreover,

Andersson indicates that the microfluidic device can comprise more than one reaction chamber and more than one separation channel. Accordingly, one of ordinary skill in the art would have been guided by Andersson to incorporate a separate chamber or channel for each step described by Patricelli. Moreover, Andersson's device is specifically conditioned to prepare a sample for mass spectrometry analysis. Accordingly, the skilled artisan would have had a reasonable expectation of success.

ii. Claim 12 is obvious

Since Patricelli teaches that the steps are performed in sequence, it would have been obvious to one of ordinary skill in the art to configure the reaction chambers and channels in Andersson's device to be in series, thereby accommodating Patricelli's sequential steps.

Claims 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patricelli, cited above, in view of Toyo'oka *et al*. (Anal. Chem., vol. 56, pp. 2461-2464 (1984)) ("Toyo'oka").

Patricelli does not describe 4-(aminosulfonyl)-7-fluoro-2,1,3-benzoxadiazole (ABD-F).

Toyo'oka describes ABD-F as an appropriate fluorogenic reagent that can specifically bind to thiol groups, is highly reactive and has good stability. *See* page 2461, abstract and page 2464, left column, second to last paragraph.

Given the foregoing description, it would have been obvious to one of ordinary skill in the art to modify Patricelli's method to include Toyo'oka's ABD-F as the

fluorescent label. The skilled artisan would have been motivated to perform the modification based on Toyo'oka's description that ABD-F can specifically bind to thiols and is highly reactive and has good stability. Moreover, since Patricelli indicates that any fluorescent moiety can be used, the skilled artisan would have had a reasonable expectation of success in combining Toyo'oka's ABD-F with Patricelli's method.

Claims 16-18, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patricelli, cited above.

i. Claim 16 is obvious

Patricelli, in addition to the subject matter described above, discloses performing the labeling, separation, digestion and MS identification steps on two or more distinct samples. *See* column 3, lines 30-47.

Patricelli, however, does not explicitly teach an HPLC equipped with a fluorescence detector.

Given the foregoing description, it would have been obvious to one of ordinary skill in the art to combine Patricelli's fluorescence detector and HPLC. Patricelli indicates that both devices are used during the separation step, as described above. Moreover, "equipped" as claimed can simply include attaching the HPCL and fluorescent detector together such that the detector detects eluted fractions from the HPLC – a task that would involve mere routine skill in the art. Indeed, the specification does not limit "equipped" in any manner. Accordingly, the skilled artisan would have

been guided by Patricelli to place the HPLC and fluorescent detector together. For the same reasons, the skilled artisan would have had a reasonable expectation of success.

ii. Claims 17-18 and 20 are obvious

Regarding claims 17 and 18, since Patricelli teaches that two quantitative values can be compared, it would involve only routine skill in the art to take a ratio of the two values. Accordingly, the claimed "ratio" step is obvious.

Regarding claim 20, Patricelli teaches biological samples, including cells and tissues. *See* column 5, lines 38-51.

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Patricelli, cited above, in view of U.S. Patent App. Pub. No. 2007/0065343 to Srinivasan ("Srinivasan").

Patricelli teaches employing internal standards comprising fluorescent moieties that are different from those used to label the sample. *See* column 18, lines 30-34. Since the standards are internal, they are considered to be mixed with the sample, thereby teaching "sample A and sample B are combined." Patricelli also describes mass spectrometry, as described above.

Patricelli, however, does not teach that the combined sample is "applied to two HPLC," as claimed.

Srinivasan describes a method of performing multiple chromographic elutions of a sample, in order to increase sensitivity for a particular analyte of interest. *See* page 2, paragraphs 0013 and 0014.

Given the foregoing description, it would have been obvious to one of ordinary skill in the art to modify Patricelli's method with Srinivasan's sequential chromatographic elutions. The skilled artisan would have been motivated to perform the modification since Srinivasan teaches that performing multiple chromatographic elutions will increase the sensitivity of the assay. Moreover, since Patricelli teaches chromatographic elutions, the skilled artisan would have had a reasonable expectation of success in adding an extra chromatographic elution.

Allowable Subject Matter

Claim 21 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Response to Arguments

Applicants traverse the rejection of the pending claims. *See* Response filed October 6, 2009. Applicants focus the traversal on the allegation that the Patricelli reference does not teach a HPLC/fluorescence detection before a digestion. *See* pages 11-12. Applicants specifically point to a quote from Patricelli: "the labeled ABP-active target protein conjugates are most preferably proteolytically digested prior to the next stage of enrichment and/or analysis." *See* page 11. Applicants opine that this quote definitively states that digestion is only performed before enrichment or analysis. A fair reading of this quote, however, reveals the opposite. Indeed, the term "preferably"

indicates that the digestion should be performed before enrichment or analysis, but that it can also be performed after enrichment or analysis. The order of performing digestion and enrichment/analysis is therefore not set in stone. Accordingly, Patricelli is not "silent" with respect to separation prior to digestion, as stated by Applicants. Consequently, Applicants' argument is not found convincing.

Conclusion

Claims 1-7, 9-20, 23 and 26 are rejected. Claim 21 is objected to.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leon Y. Lum whose telephone number is (571) 272-

2872. The examiner can normally be reached on Monday to Friday (8:30 am to 5:00 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark L. Shibuya can be reached on (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon Y. Lum/
Examiner, Art Unit 1641

/Unsu Jung/
Primary Examiner, Art Unit 1641